FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)
PU3682USW	10/009704

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/11418	April 28, 2000	April 30, 1999

TITLE OF INVENTION

Method and System for Detecting Trace Minerals in Cryogenic Liquids

APPLICANT(S) FOR DO/EO/US

WALKER, Dwight Sherod and MASCHO, John Anderson, Jr.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Copy of PCT Request
Copy of PCT Cover Letter

Express Mail Label No.: EL395892697US

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR) 10/009704	INTERNATIONAL APPLICATION NO. PCT/US00/11418	ATTORNEY'S DOCKET NUMBER PU3682USW

531 Rec'd PCT/ 29 OCT 2001

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**	
☒	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**	
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**	
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**	
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**	
	ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**
	Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	29 - 20 =	9	x $18.00	**$162.00**
Independent claims	4 - 3 =	1	x $84.00	**$84.00**
Multiple Dependent Claims **(check if applicable).**			☐	**$0.00**

TOTAL OF ABOVE CALCULATIONS =	**$1,136.00**
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.	**$0.00**
SUBTOTAL =	**$1,136.00**
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +	**$0.00**
TOTAL NATIONAL FEE =	**$1,136.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐	**$0.00**
TOTAL FEES ENCLOSED =	**$1,136.00**
Amount to be: refunded	$
charged	$

a. ☐ A check in the amount of _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **07-1392** in the amount of **$1,136.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **07-1392** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

23347
PATENT TRADEMARK OFFICE

SIGNATURE

Charles E. Dadswell
NAME

35,851
REGISTRATION NUMBER

10/29/01
DATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: WALKER, Dwight Sherod, et. al.
International Application No.: PCT/US00/11418
International Filing Date: April 28, 2000
Title: METHOD AND SYSTEM FOR DETECTING TRACE MINERALS IN CRYOGENIC LIQUIDS

Commissioner of Patents
Washington, D.C. 20231

FIRST PRELIMINARY AMENDMENT

Dear Sir:

The above identified application is being transmitted herewith for entry in the US National Phase under Chapter II of the PCT for the purpose of adding the priority information.

In the Abstract:

Please substitute the attached Abstract, which has been placed on a separate sheet of paper according to US practice, as required under 37 CFR 1.72(b)

In the Specification:

On the first line of the specification, after the Title, please add:

--This application is filed pursuant to 35 U.S.C. §371 as a United States National Phase Application of International Application No. **PCT/US00/11418** filed **April 28, 2000**, which claims priority from **60/132,042** filed **April 30, 1999** in the United --

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EL395892697US

REMARKS

Applicants have attached an abstract on a separate sheet of paper as required by US practice. Applicants have amended the specification for purposes of adding the priority information. It is respectfully submitted that the present application is in condition for allowance. An early consideration and notice of allowance are earnestly solicited.

Respectfully submitted,

Date: October 29, 2001

By: ____________________

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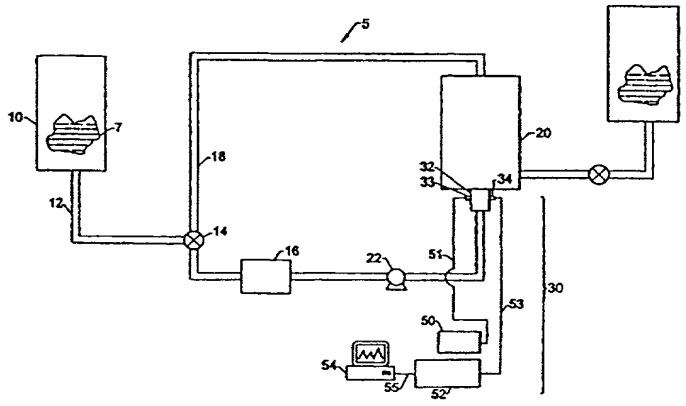
METHOD AND SYSTEM FOR DETECTING TRACE MATERIALS IN CRYOGENIC LIQUIDS

ABSTRACT

A method for qualitative and quantitative determination of trace impurities in a cryogenic liquid, comprising the steps of (i) measuring the absorption spectrum of the cryogenic liquid by passing light in the infrared region through the cryogenic liquid, the cryogenic liquid absorption spectrum having a first reference energy, (ii) measuring the absorption spectrum of at least one impurity alone by passing light in the infrared region through the impurity, (iii) passing a cryogenic liquid sample into a flow cell, wherein the maximum pressure drop of the cryogenic liquid sample across said flow cell is in the range of 0.5 to 5.0 lb./in.^{2}, (iv) measuring the absorption spectra of the cryogenic liquid sample by passing light in the infrared region through the cryogenic liquid sample while the cryogenic liquid sample is within the cell, (v) comparing the cryogenic liquid sample absorption spectra to the cryogenic liquid and impurity spectra, (vi) confirming the presence of the sample absorption spectrum associated with the impurity, the sample absorption spectrum associated with the impurity having a second reference energy, and (vii) determining the concentration (C) of the impurity in the cryogenic liquid sample by the following relationship,

$$kC = \log \frac{\text{second reference energy}}{\text{first reference energy}}$$

where k is a fixed proportionality constant.



METHOD AND SYSTEM FOR DETECTING TRACE MATERIALS IN CRYOGENIC LIQUIDS

FIELD OF THE PRESENT INVENTION

The present invention relates generally to a system for detecting trace materials in cryogenic liquids. More particularly, the invention relates to a method and system for detecting trace amounts of a material or component in cryogenic liquids by means of infrared spectroscopic analysis.

BACKGROUND OF THE INVENTION

A "cryogenic liquid" is generally defined as a fluid which would be a vapor under ambient conditions of temperature and pressure. Typical examples of cryogenic liquids include liquid oxygen, liquid nitrogen, liquid argon, liquid methane, liquid helium, liquid neon, liquid hydrogen and liquid fluorinated hydrocarbons (i.e., Freon®).

Cryogenic liquids are employed in a variety of applications, such as coolants, cleaning agents and polymer transfer agents. In pharmaceutical inhalation systems, the inhalation formulation (i.e., active ingredient) is typically carried to the patient in an aerosol propellant stream of chemically inert and biologically safe material. The most commonly employed propellants are fluorinated hydrocarbons.

Cryogenic liquids are often produced by the cryogenic distillation of a feed, such as air, in a cryogenic distillation plant comprising one or more cryogenic distillation columns. In order to ensure that the plant is operating properly and also to ensure that product of

requisite purity is being produced, samples of the cryogenic liquid must be routinely obtained and analyzed.

After production, the cryogenic liquids are transported from the production facility to the new site, generally in cylinders or tanker trucks. The cryogenic liquids are then often stored at the use site in storage tanks. In order to ensure that the cryogenic liquid has not been contaminated in transportation and/or storage, additional samples of the cryogenic liquid are typically obtained and analyzed.

Further, in the event of a cryogenic liquid being employed as a pharmaceutical propellant, since the propellant and inhalation formulation are introduced directly into a patient's lungs, it is absolutely imperative that the propellant be free of residual components and contaminants (i.e., impurities). Such materials generally arise during general maintenance and/or cleaning of the drug delivery lines. Thus, after maintenance and/or cleaning of the lines, the propellant must be analyzed to detect the presence of any trace materials.

Various methods (and systems) have been employed to ensure that a cryogenic liquid is free of residual components or contaminants. However, as discussed below, the conventional methods have several drawbacks and/or disadvantages.

One method of sampling a cryogenic liquid is the batch technique wherein a sample of the cryogenic liquid is caused to flow into a capture device or cell. The flow of cryogenic liquid is then shut off and the sample is warmed to produce a gas, which is passed on to one or more analyzers. Typical analyzers include a gas chromatograph, a paramagnetic oxygen analyzer or an electro-chemical oxygen analyzer.

The batch method is disadvantageous for several reasons. First, a large amount of sample is vented and thus lost. Second, the batch capture system is complicated and costly. Third, and perhaps most important, the batch technique is inherently limited in timeliness of the information obtained.

Another method of sampling a cyrogenic liquid involves the coupling of an analyzer system to a cyrogenic liquid source via a conduit which is sufficiently long to enable the cryogenic liquid to vaporize prior to reaching the analyzer or analyzers. Two major problems arise with this continuous sampling method. First, the vaporization of the cyrogenic liquid in the conduit results in local pressure increases, which cause liquid to flow back out of the conduit and into the cyrogenic liquid source.

Another problem with the continuous method is that the requisite long conduit affords an opportunity for a significant amount of trace impurities within the sample to plate onto the inside surface of the conduit. Still further, the long conduit results in a long response time from the acquisition of the sample to the analysis itself.

It is therefore an object of the present invention to provide an improved method and system for sampling cryogenic liquids.

It is another object of the present invention to provide a simple, accurate and reliable method of detecting trace materials in cryogenic liquids.

It is another object of the invention to provide a method and system for detecting trace materials in cryogenic liquids at multiple locations within a production environment.

It is yet another object of the invention to provide a method of continuous sampling and analyzing of a cyrogenic liquid by means of near infrared spectroscopy.

SUMMARY OF THE INVENTION

In accordance with the above objects and those that will be mentioned and will become apparent below, the method of detecting a trace material in a cryogenic liquid in accordance with this invention comprises the steps of (i) measuring the absorption spectrum of the cryogenic liquid by passing light in the infrared region through the cryogenic liquid, said cryogenic liquid absorption spectrum having a first reference energy, (ii) measuring the

absorption spectrum of at least one impurity alone by passing light in the infrared region through said impurity, (iii) passing a cryogenic liquid sample into a flow cell, wherein the maximum pressure drop of the cryogenic liquid sample across said flow cell is in the range of 0.5 to 5.0 lb./in.^{2}, (iv) measuring the absorption spectra of the cryogenic liquid sample by passing light in the infrared region through the cryogenic liquid sample while the cryogenic liquid sample is within the cell, (v) comparing the cryogenic liquid sample absorption spectra to the cryogenic liquid and impurity spectra, (vi) confirming the presence of the sample absorption spectrum associated with the impurity, the sample absorption spectrum associated with the impurity having a second reference energy, and (vii) determining the concentration (C) of said impurity in the cryogenic liquid sample by the following relationship,

$$kC = \log \frac{\text{second reference energy}}{\text{first reference energy}}$$

where k is a fixed proportionality constant.

The system of the invention comprises (i) source of cryogenic liquid sample, (ii) conduit means in flow communication with the source of cryogenic liquid sample for transferring the cryogenic liquid sample to a plurality of locations, (iii) at least one flow cell in flow communication with the conduit means, the flow cell being adapted to maintain a maximum pressure drop across the cell in the range of 0.5 to 5.0 lb./in.^{2}, (iv) analyzer means for respectively measuring the absorption intensity of the base cryogenic liquid, target impurity and cryogenic liquid sample by separately passing near infrared light through the base cryogenic liquid, impurity and cryogenic liquid sample, (v) means for comparing the absorption intensities of the base cryogenic liquid, impurity and cryogenic liquid sample to determine the presence of the impurity in the cryogenic liquid sample, and (vi) means for determining the concentration of the impurity.

BRIEF DESCRIPTION OF THE DRAWINGS

Further features and advantages will become apparent from the following and more particular description of the preferred embodiments of the invention, as illustrated in the accompanying drawings, and in which like referenced characters generally refer to the same parts or elements throughout the views, and in which:

FIGURE 1 is a schematic illustration of a pharmaceutical mixing and delivery system employing the sampling and analysis system of the present invention;

FIGURE 2 is a partial section plan view of a mixing chamber and flow cell of the present invention;

FIGURE 3 is a plan view of a cryogenic liquid storage column employing the sampling system of the present invention;

FIGURE 4 is a schematic illustration of a production facility employing an additional embodiment of the sampling and analysis system of the present invention; and

FIGURE 5 are absorption curves for methanol measured in an embodiment of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention substantially reduces or eliminates the disadvantages and shortcomings associated with prior art cryogenic liquid sampling and analysis methods. As discussed in detail below, the present invention provides for simple, accurate and reliable continuous sampling and analysis of a cryogenic liquid to determine the presence and identity of trace components and/or contaminants. By the term "cryogenic liquid", as used herein, it is meant to mean a liquid that would be a vapor at a temperature of 15°-25°C at 1.0 atmosphere. The term "cryogenic liquid" thus includes liquid oxygen, liquid nitrogen, liquid argon, liquid methane, liquid helium, liquid neon, liquid hydrogen, and liquid fluorinated

hydrocarbons, including, hydrofluorocarbons, chlorofluorocarbons, hydrofluoroalkanes and derivatives thereof.

The terms "components", "contaminants" and "impurities", as used herein, are meant to include (i) materials having vibration energies in the range of 3 x 10e14-12e14Hz, (ii) materials containing OH, CH, SH, CO and NH bonds and (iii) volatile organics.

As indicated above, the conventional cryogenic liquid sampling methods and systems have numerous drawbacks and/or disadvantages. The methods and systems are generally complex, inherently limited in timeliness and limited in location of sampling (e.g., site). In contrast to the conventional systems, applicant's method and system provides prompt, accurate data and is readily adaptable to any location (or multiple locations) within the production environment, including the cryogenic liquid delivery lines.

Referring to Figure 1, there is shown a simplified representation of a pharmaceutical mixing and delivery system 5 employing the sampling system 30 of the present invention. The mixing and delivery system 5 includes a cryogenic liquid (i.e., Freon®) reservoir 10 for containing the cryogenic liquid material 7, a cryogenic liquid feed line 12, a feed valve 14, a filling unit 16, a recirculation line 18, a mixing chamber 20, which facilitates mixing of the cryogenic liquid and the pharmaceutical formulation, and a pump 22.

The sampling (and analysis) system 30 of the invention includes a flow cell 32 an analyzer 52 to determine the presence and identity of trace components and/or contaminants (i.e., impurities) in the cryogenic liquid 7 and processing means 54 to control the analyzer and process data therefrom. In a preferred embodiment, the analyzer 52 comprises an infrared spectroscopic analyzer.

It is well known that when the molecules are exposed to electromagnetic rays (i.e., infrared light) of a wavelength which has a photon energy equivalent to their value of the vibration energy level, the molecules absorb the electromagnetic waves as their own vibration energy. The amount of absorption is proportionate to the abundance of the

molecules present. When this vibration energy level value is converted to photon energy, ordinarily, it will correspond to wavelengths in the infrared region.

Accordingly, as discussed in detail below, when infrared light from the light source 50 is passed through the cryogenic liquid 7 (i.e., sample) within the flow cell 32 (see Fig. 2), each trace material (i.e., component and contaminant) contained in the cryogenic liquid will exhibit a distinctive absorption spectrum. The identity of a selective one of the trace materials (i.e., target impurity) is then determined from the absorption spectrum (i.e., the wavelength of the light absorbed) associated with the target impurity. Further analysis of the absorption spectra (e.g., quantitative determination) is achieved by virtue of the processing means 54 of the invention, which, in a preferred embodiment, comprises a computer.

Referring back to Figure 1, the flow cell 32 of the invention is preferably in flow communication with the mixing chamber 20. According to the invention, the flow cell 32 provides substantially uniform and continuous flow of the cryogenic liquid (with and without the pharmaceutical formulation) therethrough with a maximum pressure drop across the flow cell 32 in a range of 0.5 to 5.0 lb./in.^{2}, preferably 0.75 to 1.5 lb./in.^{2}. More preferably, the maximum pressure drop is approximately 1.0 lb./in.^{2}.

According to the invention, the flow cell 32 is preferably constructed of copper, stainless steel, or another like material and is vacuum insulated to ensure that the cryogenic liquid 7 remains in its liquid state (i.e., does not vaporize). In additional envisioned embodiments, the flow cell 32 includes cooling means (shown in phantom in Figure 2) comprising a cell liner 38 and control means 39 to control the temperature of the cryogenic liquid 7 within the flow cell 32.

As illustrated in Figures 1 and 2, the flow cell 32 further includes couplings 33, 34, which are adapted to receive a light source line 51 and analyzer line 53, respectively. The couplings 33, 34 are further adapted to facilitate communication by and between (i) the light source line 51 and tungsten halogen lamp 35 and (ii) analyzer line 53 and analyzer probe 36, respectively.

As indicated above, an advantage of applicant's system is that the flow cell 32 and, hence, the system is readily adaptable to virtually any location of cryogenic liquid flow within a production environment. Such locations include pharmaceutical delivery lines, such as those illustrated in Figures 1 and 2, and a transfer line 42 proximate a storage tank or column 40, as illustrated in Figure 3. Thus, multiple flow cells 32 may be disposed at various key locations within a production environment to provide random or continuous analysis of the cryogenic liquid.

Referring to Figure 4, there is shown a schematic illustration of a simple production facility employing a multiple cell system of the invention. The production facility is housed within a building structure 60 and includes a cryogenic liquid storage column 62, disposed externally of the building structure 60, a delivery line 64 (adapted to provide product, denoted by Arrow P), a valve 65, a plurality of pumps 66a, 66b in flow communication with the delivery line 64, a mixing chamber 68 and a component feed line 70 (adapted to feed a component into the mixing chamber 68, denoted by Arrow I). The facility further includes a plurality of flow cells 32a, 32b and the light source 50, analyzer 52 and processing means 54 of the invention.

In the noted embodiment, the light source 50 includes two light source lines 51a, 51b. The light source lines 51a, 51b are in communication with cells 32a and 32b, respectively.

The analyzer 52 of the invention is similarly provided with two analyzer lines 53a, 53b. The analyzer lines 53a, 53b are also in communication with cells 32a and 32b, respectively.

In additional envisioned embodiments, a plurality of analyzers 52, 52a (shown in phantom) are employed. In this embodiment, analyzer line 53c is directly connected to cell 32b and an additional processing means line 55a is employed.

According to the invention, data from each respective cell 32a, 32b (i.e., location) is selectively acquired and processed by the processing means 54 of the invention, which is in

communication with the analyzer 52 via processing means line 55 (or analyzers 52, 52a via processing means lines 55, 55a).

As stated above, the analyzer 52 of the invention is adapted to determine the presence of trace components and contaminants in the cryogenic liquid. According to the invention, the determination of a trace component or contaminant is preferably accomplished by conducting a first scan of the base cryogenic liquid to establish a first absorption spectrum having a first reference energy (i.e., absorption energy). A second scan of at least one target material (i.e., component or contaminant) is then conducted to determine an impurity absorption spectrum associated with the target material. The first and second scans preferably comprising near infrared light in the range of 900-2200 nanometers.

The first absorption spectrum and impurity absorption spectrum (or spectra) are then stored in the processing means 54 memory. During on-line analysis, the cryogenic liquid sample is scanned while the sample is contained in a selected cell (i.e., 37, 32a, 32b) to obtain the sample absorption spectra. The sample absorption spectra are then compared to the stored absorption spectra via the processing means 54 to distinguish among and confirm the presence of the cryogenic liquid sample absorption spectrum associated with the target material, the sample absorption spectrum associated with the impurity having a second reference energy. The method thus provides accurate and reliable identification of a trace material in a cryogenic liquid sample.

According to the invention, further analysis and/or processing of the stored absorption spectra and the sample absorption spectra is provided by the processing means 54 of the invention. Such additional analysis includes a determination of the concentration of the component or contaminant, and component and contaminant concentration profile(s) at selected cell locations.

The concentration (C) of the component or contaminant is preferably determined as follows:

$$kC = \log \underline{E}_2$$

E_1

where:

E_1 = reference energy (i.e., absorption energy) of the base cryogenic liquid absorption spectrum;

E_2 = reference energy of the sample absorption spectrum associated with the target material; and

k = fixed proportionality constant.

To demonstrate the superior performance of applicant's method and system, a sample of Freon® was spiked with known concentrations of methanol. Methanol, an organic solvent, is typically employed to flush pharmaceutical filling lines between different product runs. The solutions were then introduced into the mixing chamber 20 and ultimately into the flow cell 32.

Near infrared light (NIR) in the range of 900-2200 nanometers was then passed through the sample within the flow cell 32. The resultant infrared absorption spectra (i.e., absorption curves), which were obtained using a Rosemount Analytical AOTF-NIR analyzer, are shown in Figure 5.

As illustrated in Figure 5, methanol and, hence, impurity concentrations of less than 0.01% are readily detected, distinguished and determined by the method and system of the invention. Such sensitivity in "in-situ" liquid analysis is unparalleled in the art.

The results of the trace determination experiment further indicate that trace amounts of an impurity—component and/or contaminant—can be accurately detected and quantified "on-line" at levels well below the pharmaceutical industry standard of ≤ 0.02%. The results were also achieved in a fraction of the time generally required for prior methods and systems.

Without departing from the spirit and scope of this invention, one of ordinary skill can make various changes and modifications to the invention to adapt it to various usages and

conditions. As such, these changes and modifications are properly, equitably, and intended to be, within the full range of equivalence of the following claims.

CLAIMS

What is Claimed is:

1. A method for identifying impurities in a cryogenic liquid, comprising the steps of:

measuring the absorption spectrum of the cryogenic liquid;

measuring the absorption spectrum of at least one impurity alone;

passing a cryogenic liquid sample into a flow cell;

measuring the absorption spectra of said cryogenic liquid sample while said cryogenic liquid sample is within said cell;

comparing said cryogenic liquid sample absorption spectra to said cryogenic liquid and impurity spectra; and

confirming the presence of said sample absorption spectrum associated with said impurity.

2. The method of Claim 1, wherein maximum pressure drop across said flow cell is in the range of 0.5 to 5.0 lb./in.^{2}.

3. The method of Claim 2, wherein said maximum pressure drop across said flow cell is in the range of 0.75 to 1.5 lb./in.^{2}.

4. The method of Claim 1, wherein said absorption spectra of said cryogenic liquid, impurity and cryogenic liquid sample is measured by passing light in the infrared region through said cryogenic liquid, impurity and cryogenic liquid sample.

5. The method of Claim 4, wherein said light to be passed through said cryogenic liquid, impurity and cryogenic liquid sample is scanned in the range of 900 to 2200 nanometers.

6. The method of Claim 1, wherein said cryogenic liquid comprises a liquid fluorinated hydrocarbon selected from the group consisting of a hydrofluorocarbon, chlorofluorocarbon, hydrofluoroalkane and derivatives thereof.

7. The method of Claim 1, wherein said impurity comprises a material having at least a CO, NH, OH, CH and SH bond.

8. The method of Claim 1, wherein said impurity comprises a material having a vibration energy in the range of approximately 3 x 10e14-12e14Hz.

9. The method of Claim 1, wherein said impurity comprises a volatile organic.

10. A method for identifying impurities in a cryogenic liquid, comprising the steps of:

measuring the absorption spectrum of the cryogenic liquid by passing light in the infrared region through the cryogenic liquid, said cryogenic liquid absorption spectrum having a first reference energy;

measuring the absorption spectrum of at least one impurity alone by passing light in the infrared region through said impurity;

passing a cryogenic liquid sample into a flow cell, wherein the maximum pressure drop of said cryogenic liquid sample across said flow cell is in the range of 0.75 to 1.5 lb/in.^{2};

measuring the absorption spectra of said cryogenic liquid sample by passing light in the infrared region through said cryogenic liquid sample while said cryogenic liquid sample is within said cell;

comparing said cryogenic liquid sample absorption spectra to said cryogenic liquid and impurity spectra;

confirming the presence of said cryogenic liquid sample absorption spectrum associated with said impurity, said sample absorption spectrum associated with said impurity having a second reference energy; and

determining the concentration (C) of said impurity in said cryogenic liquid sample by the following relationship,

$$kC = \log \frac{\text{second reference energy}}{\text{first reference energy}}$$

where k is a fixed proportionality constant.

11. The method of Claim 10, wherein said flow cell provides substantially continuous flow of said cryogenic liquid sample through said flow cell.

12. The method of Claim 10, wherein said maximum pressure drop across said flow cell is approximately 1.0 lb./in.^{2}.

13. The method of Claim 10, wherein said light to be passed through said cryogenic liquid, impurity and cryogenic liquid sample is scanned in the range of 900 to 2200 nanometers.

14. The method of Claim 10, wherein said cryogenic liquid comprises a liquid fluorinated hydrocarbon selected from the group consisting of a hydrofluorocarbon, chlorofluorocarbon, hydrofluoroalkane and derivatives thereof.

15. The method of Claim 10, wherein said impurity comprises a material having at least a CO, NH, OH, CH and SH bond.

16. The method of Claim 10, wherein said impurity comprises a material having a vibration energy in the range of approximately 3 x 10e14-12e14Hz.

17. The method of Claim 10, wherein said impurity comprises a volatile organic.

18. A method for identifying impurities in a cryogenic liquid at multiple locations within a production environment, comprising:

measuring the absorption spectrum of the cryogenic liquid by passing light in the infrared region through said cryogenic liquid, said cryogenic liquid absorption spectrum having a first reference energy;

measuring the absorption spectrum of at least one impurity alone by passing light in the infrared region through said impurity;

passing a cryogenic liquid sample into each of a plurality of flow cells, wherein the maximum pressure drop of said samples across said flow cells is in the range 0.5 to 5.0 lb./in.^{2}, each of said flow cells corresponding to a location within the production environment;

selectively measuring the absorption spectra of said cryogenic liquid samples by passing light in the infrared region through said cryogenic liquid samples while said samples are contained within flow cells;

comparing said cryogenic liquid sample absorption spectra to said cryogenic liquid and impurity spectra;

confirming the presence of said sample absorption spectrum associated with said impurity, said sample absorption spectrum associated with said impurity having a second reference energy; and

determining the concentration (C) of said impurity in said cryogenic liquid sample at each of said cell locations by the following relationship,

$$kC = \log \frac{\text{second reference energy}}{\text{first reference energy}}$$

where k is a fixed proportionality constant.

19. The method of Claim 18, wherein maximum pressure drop across said flow cells is in the range of 0.75 to 1.5 lb./in.^{2}.

20. The method of Claim 18, wherein said maximum pressure drop across said flow cells is approximately 1.0 lb./in.^{2}.

21. The method of Claim 18, wherein said light to be passed through said cryogenic liquid, impurity and cryogenic liquid samples is scanned in the range of 900 to 2200 nanometers.

22. The method of Claim 18, wherein said cryogenic liquid comprises a liquid fluorinated hydrocarbon selected from the group consisting of a hydrofluorocarbon, chlorofluorocarbon, hydrofluoroalkane and derivatives thereof.

23. The method of Claim 18, wherein said impurity comprises a material having at least a CO, NH, OH, CH and SH bond.

24. The method of Claim 18, wherein said impurity comprises a material having a vibration energy in the range of approximately 3 x 10e14-12e14Hz.

25. The method of Claim 18, wherein said impurity comprises a volatile organic.

26. A system for sampling a plurality of cryogenic liquid samples having a cryogenic liquid base, comprising:

a source of cryogenic liquid sample;

conduit means in flow communication with said source of cryogenic liquid sample for transferring said cryogenic liquid sample to a plurality of locations;

at least one flow cell in communication with said conduit means, said flow cell adapted to maintain a maximum pressure drop across said cell in the range of 0.5 to 5.0 lb./in.^{2};

analyzer means for respectively measuring the absorption intensity of the base cryogenic liquid, target impurity and cryogenic liquid sample by separately passing infrared light through the base cryogenic liquid, impurity and cryogenic liquid sample; and

means for determining the concentration of said impurity.

27. The system of Claim 26, wherein said maximum pressure drop across said cell is in the range of 0.75 to 1.5 lb./in.^{2}.

28. The system of Claim 26, wherein said system comprises a plurality of flow cells.

29. The system of Claim 28, wherein said system includes control means in communication with said analyzer means to direct said analyzer means to conduct said measurement of said cryogenic liquid sample proximate a respective one of said flow cells.

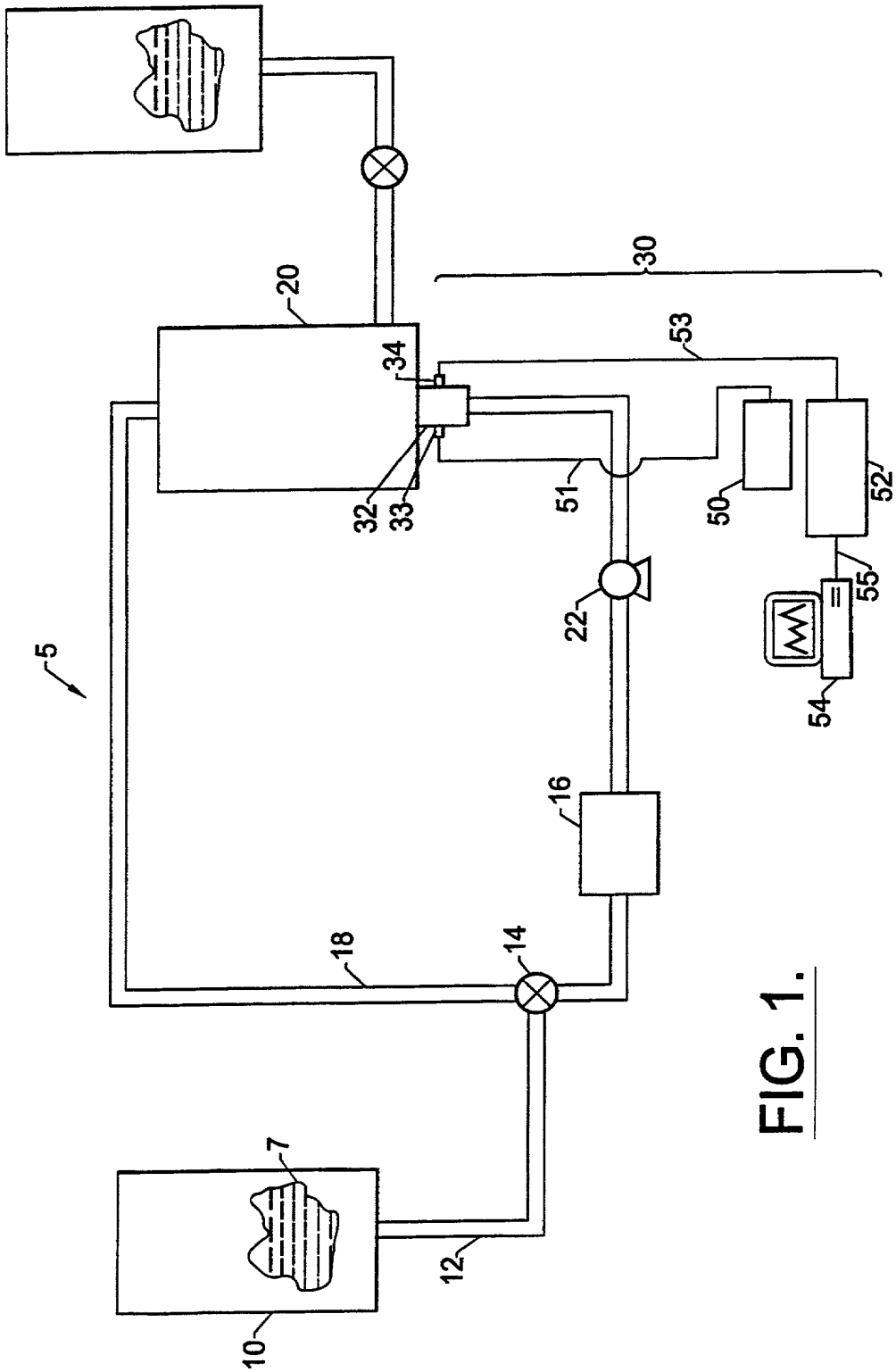


FIG. 1.

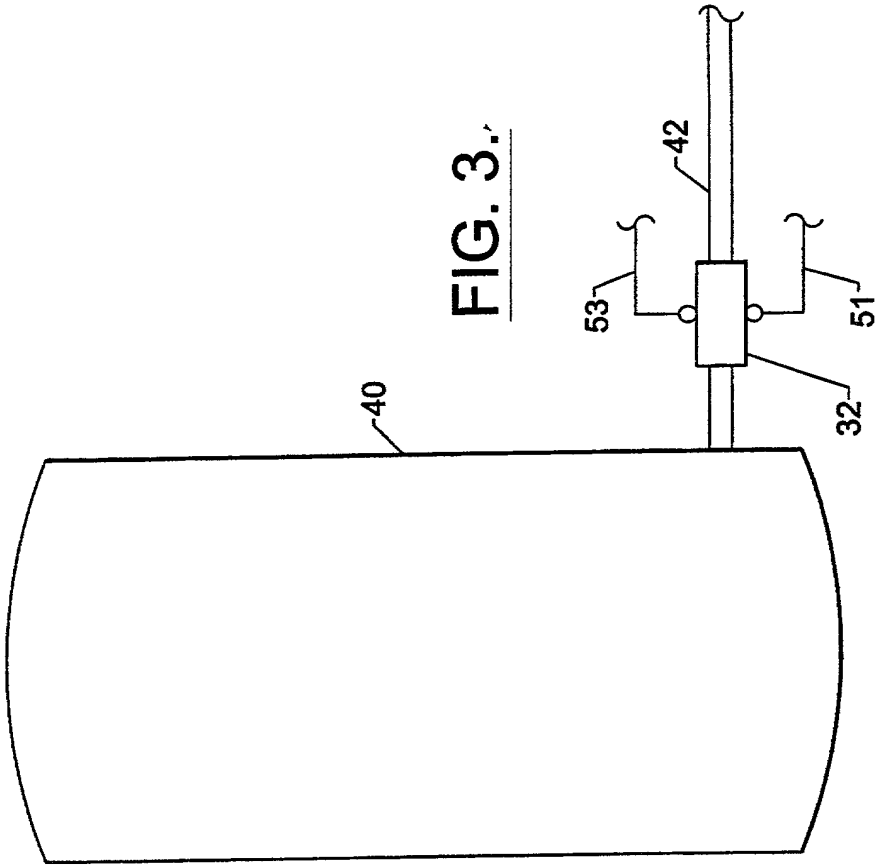


FIG. 3.

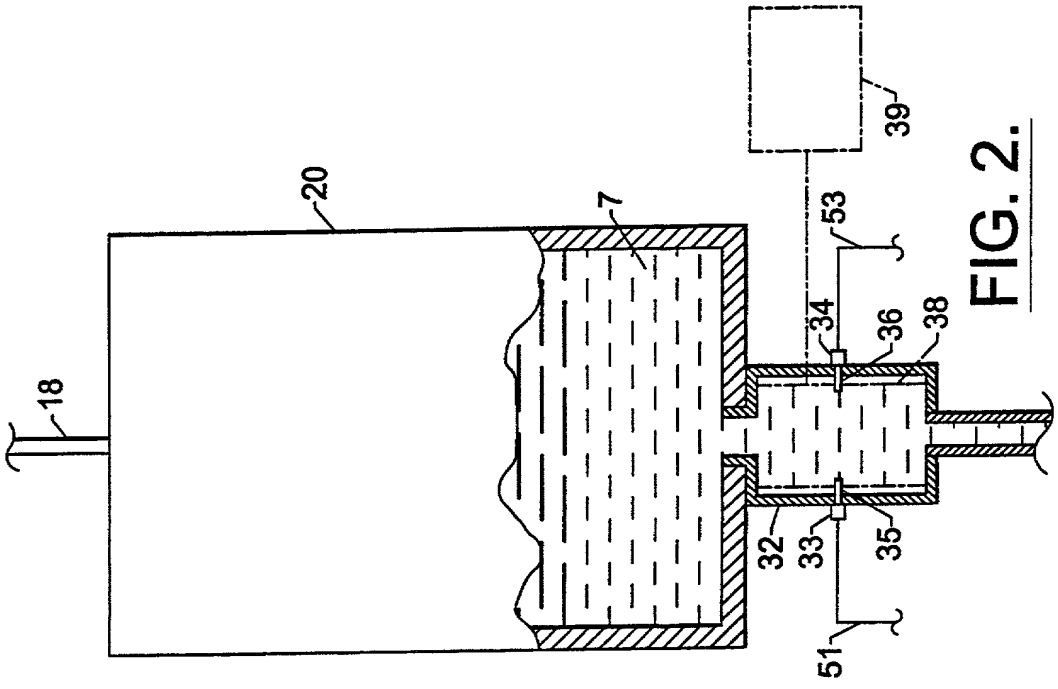
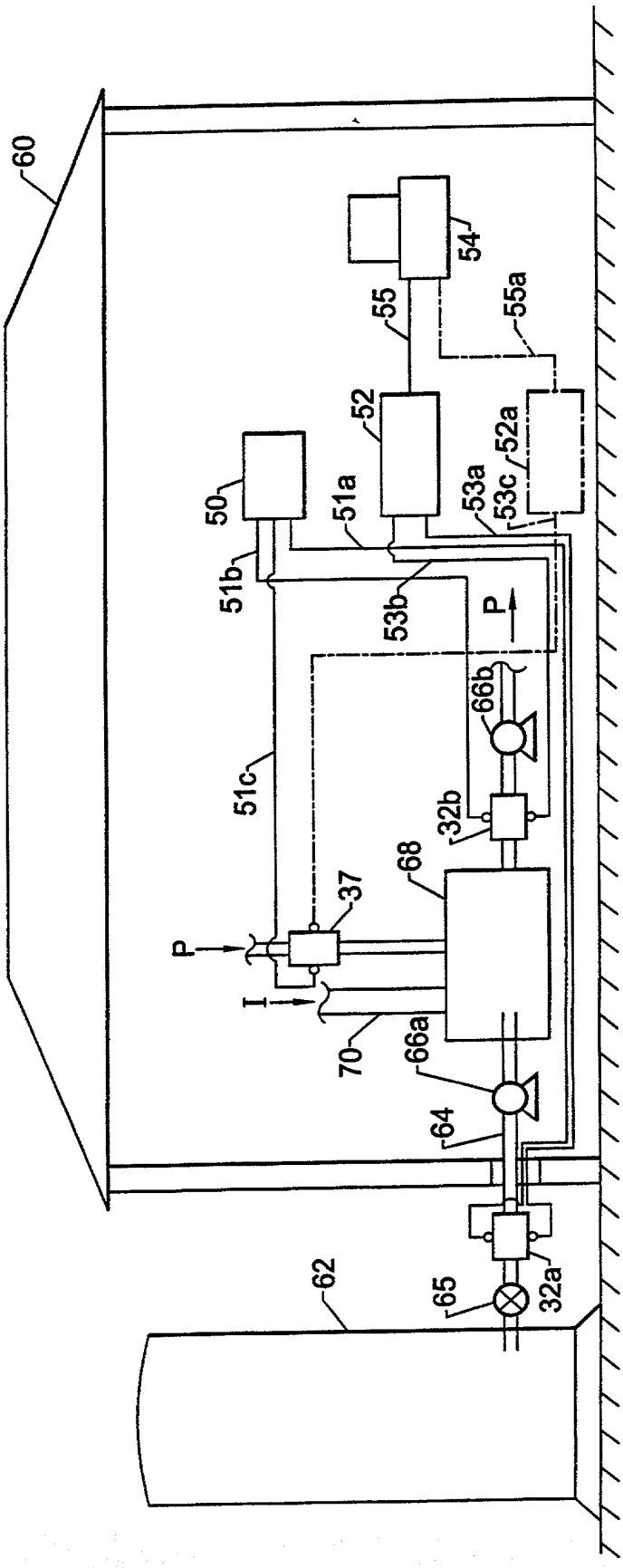


FIG. 2.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55
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52a
50
51a
53a
53c
51b
53b
P
66b
51c
32b
68
37
P
I
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64
62
65
32a

FIG. 4.

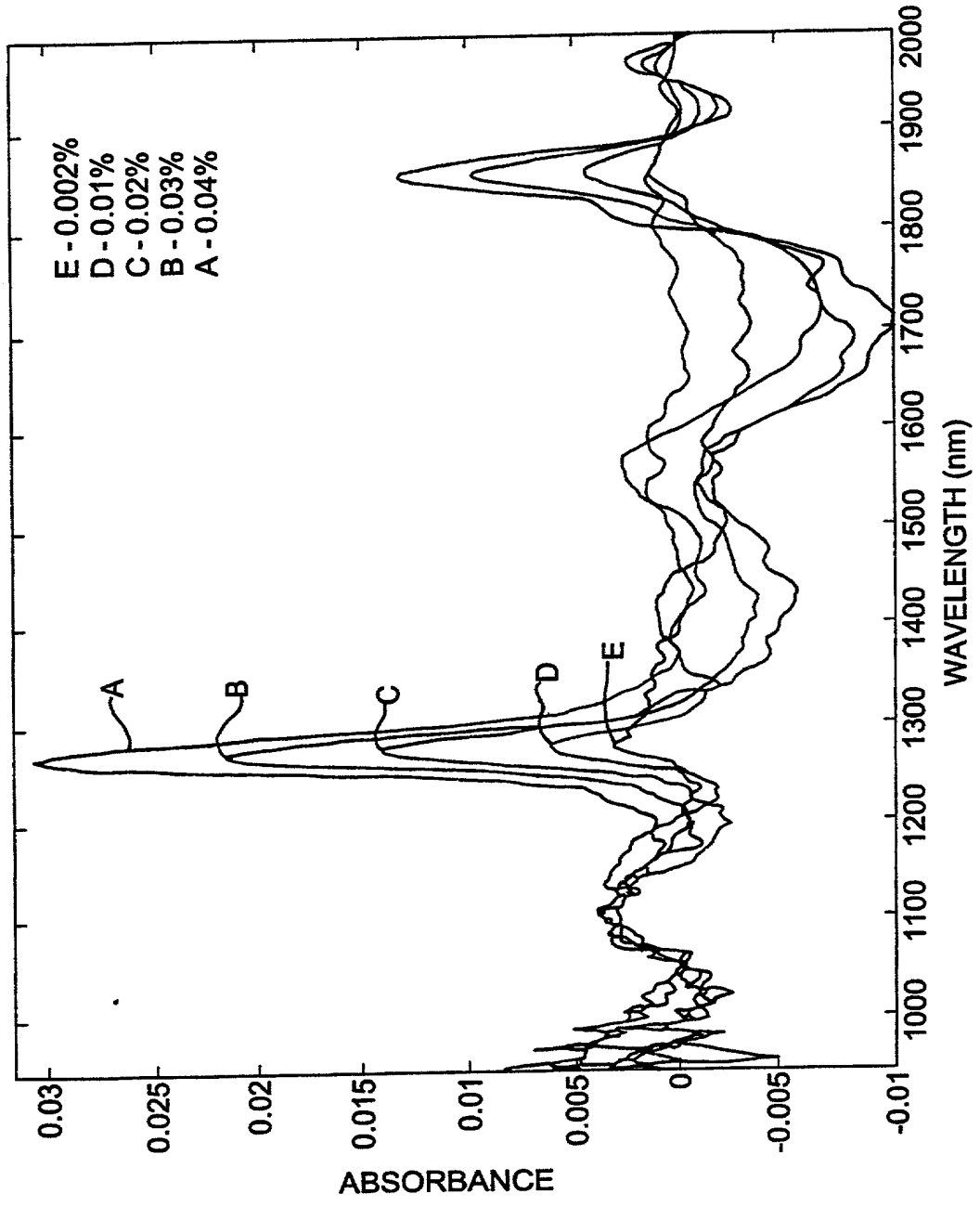
E - 0.002%
D - 0.01%
C - 0.02%
B - 0.03%
A - 0.04%
A
B
C
D
E
ABSORBANCE
0.03
0.025
0.02
0.015
0.01
0.005
0
-0.005
-0.01
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
2000
WAVELENGTH (nm)

FIG. 5.

COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY

ATTORNEY'S DOCKET
PU3682USW
First Names Inventor: Dwight Sherod WALKER
Complete if known: App No.:
Filing Date
Group Art Unit:

( ) Declaration submitted with initial filing or

( )Declaration submitted after initial filing (surcharge required 37CFR1.16(e))

As below named inventor. I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHOD AND SYSTEM FOR DETECTING TRACE MATERIALS IN CRYOGENIC LIQUIDS

the specification of which (check only one item below):

[ ]is attached hereto.

OR

[x] was filed on **28 April 2000** as United States application Serial No. _____ or **PCT** International

Application Number **PCT/US00/11418** filed and was amended on (MM/DD/YYYY) _____(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35, U.S.C. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

Prior Foreign Application Number (s)	Country	Foreign Filing Date (MM/DD/YYYY))	PRIORITY CLAIMED
1.			
2.			
3.			

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date (MM/DD/YYYY)	Priority Claimed
1. 60/132,042	30 April 1999	X
2.		
3.		
4.		
5.		

Express Mail Label No.:
EL395892697US

COMBINED DECLARATION FOR UTILITY or DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued

ATTORNEY'S DOCKET NUMBER: PU3682USW

I hereby claim the benefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. PARENT APPLICATION or PCT PARENT APPLICATION

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	STATUS (Check one) PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the U.S. Patent and Trademark Office connected therewith. (List name and registration number)

David J. Levy Reg. No. 27,655
Charles E. Dadswell Reg. No. 35,851
Karen L. Prus Reg. No. 39,337
Robert H. Brink Reg. No. 36,094
Lorie Ann Morgan Reg. No. 38,181
James P. Riek Reg. No. 39,009
Virginia C. Bennett Reg. No. 37,092
Frank P.Grassler Reg. No. 31,164
Christopher P. Rogers Reg. No. 36,334
Bonnie L. Deppenbrock Reg. No. 28,209
John L. Lemanowicz Reg. No. 37,380
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Research Triangle Park, NC 27709

23347
PATENT TRADEMARK OFFICE

Direct Telephone Calls to:
Charles E. Dadswell
919-483-6983

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

2	FULL NAME OF INVENTOR	FAMILY NAME: **WALKER**	FIRST GIVEN NAME: **Dwight**	SECOND GIVEN NAME/INITIAL: **Sherod**
	INVENTOR'S SIGNATURE	Signature:		Date: 10/19/01
0	RESIDENCE & CITIZENSHIP	CITY: **Durham**	STATE OR FOREIGN COUNTRY: **NC**	COUNTRY OF CITIZENSHIP: **US**
1	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **GlaxoSmithKline Five Moore Drive, PO Box 13398**	CITY: **Research Triangle Park**	STATE & ZIP CODE/COUNTRY: **NC 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME: **MASCHO**	FIRST GIVEN NAME: **John**	SECOND GIVEN NAME/INITIAL: **Anderson, Jr.**
	INVENTOR'S SIGNATURE	Signature:		Date:
0	RESIDENCE & CITIZENSHIP	CITY: **Durham**	STATE OR FOREIGN COUNTRY: **NC**	COUNTRY OF CITIZENSHIP: **US**
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	INVENTOR'S SIGNATURE	Signature:		Date:
0	RESIDENCE & CITIZENSHIP	CITY:	STATE OR FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP: **US**
3	POST OFFICE ADDRESS	POST OFFICE ADDRESS:	CITY:	STATE & ZIP CODE/COUNTRY:

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First Names Inventor: Dwight Sherod WALKER
Complete if known: App No.:
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[ ]is attached hereto.
OR
[x] was filed on **28 April 2000** as United States application Serial No. _____ or **PCT** International

Application Number **PCT/US00/11418** filed and was amended on (MM/DD/YYYY) _____(if applicable)

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COMBINED DECLARATION FOR UTILITY or DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued

ATTORNEY'S DOCKET NUMBER: PU3682USW

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PRIOR U.S. PARENT APPLICATION or PCT PARENT APPLICATION

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	STATUS (Check one) PATENTED	PENDING	ABANDONED

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Charles E. Dadswell Reg. No. 35,851; Virginia C. Bennett Reg. No. 37,092; John L. Lemanowicz Reg. No. 37,380
Karen L. Prus Reg. No. 39,337; Frank P.Grassler Reg. No. 31,164
Robert H. Brink Reg. No. 36,094; Christopher P. Rogers Reg. No. 36,334
Lorie Ann Morgan Reg. No. 38,181; Ralph Francis Reg. No. 38,884 (of Francis Law Group, 1808 Santa Clara Ave., Alameda, CA 94501, Telephone 510-769-9800)

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Research Triangle Park, NC 27709


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2	FULL NAME OF INVENTOR	FAMILY NAME: WALKER	FIRST GIVEN NAME: Dwight	SECOND GIVEN NAME/INITIAL: Sherod
	INVENTOR'S SIGNATURE	Signature:		Date:
0	RESIDENCE & CITIZENSHIP	CITY: Durham	STATE OR FOREIGN COUNTRY: NC	COUNTRY OF CITIZENSHIP: US
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2	FULL NAME OF INVENTOR	FAMILY NAME: ~~MASCHO~~	FIRST GIVEN NAME: John	SECOND GIVEN NAME/INITIAL: Anderson, Jr.
	INVENTOR'S SIGNATURE	Signature: X John Mascho		Date: X 10/24/01
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2	POST OFFICE ADDRESS	POST OFFICE ADDRESS: GlaxoSmithKline Five Moore Drive, PO Box 13398	CITY: Research Triangle Park	STATE & ZIP CODE/COUNTRY: NC 27709, US
2	FULL NAME OF INVENTOR	FAMILY NAME:	FIRST GIVEN NAME:	SECOND GIVEN NAME/INITIAL:
	INVENTOR'S SIGNATURE	Signature:		Date:
0	RESIDENCE & CITIZENSHIP	CITY:	STATE OR FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP: US
3	POST OFFICE ADDRESS	POST OFFICE ADDRESS:	CITY:	STATE & ZIP CODE/COUNTRY: